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Review

Potential novel pharmacological therapies for myocardial remodelling

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Left ventricular (LV) remodelling remains an important treatment target in patients after myocardial infarction (MI) and chronic heart failure (CHF). Accumulating evidence has supported the concept that beneficial effects of current pharmacological treatment strategies to improve the prognosis in these patients, such as angiotensin-converting enzyme (ACE) inhibition, angiotensin type 1 receptor blocker therapy, and β-blocker therapy, are related, at least in part, to their effects on LV remodelling and dysfunction. However, despite modern reperfusion therapy after MI and optimized treatment of patients with CHF, LV remodelling is observed in a substantial proportion of patients and is associated with an adverse clinical outcome. These observations call for novel therapeutic strategies to prevent or even reverse cardiac remodelling.

Recent insights from experimental studies have provided new targets for interventions to prevent or reverse LV remodelling, i.e. reduced endothelial nitric oxide (NO) synthase-derived NO availability, activation of cardiac and leukocyte-dependent oxidant stress pathways, inflammatory pathway activation, matrix-metalloproteinase activation, or stem cell transfer and delivery of novel paracrine factors. An important challenge in translating these observations from preclinical studies into clinical treatment strategies relates to the fact that clinical studies are designed on top of established pharmacological therapy, whereas most experimental studies have tested novel interventions without concomitant drug regimens such as ACE inhibitors or β-blockers. Therefore, animal studies may overestimate the effect of potential novel treatment strategies on LV remodelling and dysfunction, since established pharmacological therapies may act, in part, via identical or similar signalling pathways. Nevertheless, preclinical studies provide essential information for identifying potential novel targets, and their potential drawbacks, and are required for developing novel clinical treatment strategies to prevent or reverse LV remodelling and dysfunction.

1. Introduction

Left ventricular (LV) maladaptive remodelling has been consistently associated with an impaired prognosis in patients after myocardial infarction (MI) and patients with chronic heart failure (CHF),[1–3] and is thought to represent an important therapeutic target in these patients. Mechanical reperfusion therapy and current pharmacological treatment approaches can limit, to some extent, cardiac dysfunction and adverse LV remodelling in patients with an acute MI, however, LV remodelling is still observed in a substantial proportion of these patients despite modern reperfusion therapy, and is most prominent in patients with large anterior infarctions and/or microvascular dysfunction.[4–6] Recent insights into molecular mechanisms leading to LV remodelling and dysfunction, such as inflammatory pathway activation, oxidant stress pathway activation, and matrix-metalloproteinase (MMP) activation, provide potential novel targets for prevention or reversal of LV remodelling and dysfunction.

Whereas in clinical studies, LV remodelling has largely been assessed by analyzing changes in LV end-diastolic and end-systolic volumes, experimental studies have mostly analyzed the effects of novel interventions on cardiomyocyte hypertrophy, myocardial fibrosis, re-expression of an embryonic gene expression pattern, and LV dilation and dysfunction. Importantly, LV remodelling may not only lead to a progressive LV dilation and dysfunction, but may also be associated with the risk of ventricular arrhythmias.[7] Therefore, an altered LV architecture and function during post-infarction LV remodelling are likely important substrates for triggering malignant ventricular arrhythmias.

LV remodelling is thought to represent a valuable surrogate endpoint for novel therapeutic interventions in

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patients with MI or CHF. In support of this concept, beneficial effects on LV remodelling by both, pharmacological and non-pharmacological therapies have been associated with beneficial effects on prognosis in these patients. This has been observed for angiotensin-converting enzyme (ACE)-inhibitor and β-blocker therapy as described later. Furthermore, recently it was demonstrated in patients with CHF receiving cardiac resynchronization therapy, that LV reverse remodelling but not clinical improvement predicted long-term survival,[8] further supporting the concept that adverse LV remodelling represents an important therapeutic target. However, as a note of caution, like with most surrogate endpoints in clinical studies, not all therapies that were associated with a beneficial effect on LV remodelling were later associated with improved clinical outcome, suggesting that disease progression may also occur in other ways and in the absence of progressive cardiac remodelling. For example, treatment with the soluble tumor necrosis factor-α (TNF-α) antagonist etanercept improved LV remodelling and dysfunction in a study of patients with severe CHF,[9] but was later not associated with an improvement in clinical outcome in larger studies.[10] The underlying reasons for these different observations are not completely understood, but likely include potential adverse effects of TNF-α antagonism and potential beneficial effects of cytokine activation in patients with CHF.[11] In fact, most, but not all, interventions that attenuated LV remodelling had a benefical effect on survival in clinical trials. Thus, remodelling appears to represent an attractive surrogate endpoint in treatment trials but does not, of course, replace outcome trials. However, prevention of LV remodelling, *per se*, is an important target for therapeutic interventions. Specifically, interventions that attenuate LV remodelling but do not improve outcome are likely to adversely affect mortality for other and contrasting effects on a cellular or molecular level, e.g. surgical partial left ventriculectomy or surgical inhibition of LV volume expansion by implantation of a CorCap device do not provide beneficial effects probably because surgery is associated with detrimental architectural effects and/or impaired relaxation which may counteract the beneficial effects of the primary surgical target. Thus, while targeting LV remodelling should represent an attractive surrogate and target, the limitations are obvious and therefore targeting LV remodelling does no replace clinical outcome trials but rather represents a useful tool in the development of a new therapeutic intervention.

In this review, we briefly summarize the effects of current pharmacological therapies on LV remodelling and dysfunction. We then focus on potential novel pharmacological approaches to prevent or reverse LV remodelling and dysfunction based on recent insights into the molecular mechanisms leading to LV remodelling and dysfunction (*Table 1*).

Table 1 Potential novel therapeutic strategies to prevent or reverse left ventricular remodelling

Modulators of NO activity and signalling pathways
Statins
Phosphodiesterase 5A inhibitors (e.g. sildenafil)
NO enhancer
Cyclic guanylyl cyclase activator
Anti-oxidant strategies (e.g. statins, allopurinol, SOD mimetics)
Modulators of inflammation and pro-inflammatory cytokines
Metalloproteinase inhibitors
Pro-angiogenetic factors and/or cell transfer
Ryanodine receptor-stabilizing drugs
Modulators of MEF2 or HDACs
Antagomirs (micro RNAs controlling growth promoting factors)

List of potential therapeutic strategies to prevent or reverse LV remodelling, some of which are discussed in the text. HDAC denotes histone deacetylase; LV, left ventricular; NO, nitric oxide; MEF2, myocyte enhancer factor 2; SOD, superoxide dismutase.

2. Current pharmacological approaches to limit cardiac remodelling

2.1 Angiotensin-converting enzyme inhibitors/ angiotensin type 1-receptor blockers

ACE inhibitors attenuate LV remodelling in patients after MI with reduced LVEF,[12] and this has been suggested to contribute to their beneficial effects on prognosis. This concept has been strongly supported by the observation that attenuation of ventricular enlargement with the ACE inhibitor captopril was associated with a reduction in adverse events in patients after MI, suggesting a link between attenuation of LV enlargement by captopril and improved clinical outcome.[13] The VALIANT (Valsartan in Acute Myocardial Infarction Trial) echo substudy examined the effect of combined ACE-inhibitor/angiotensin type 1 (AT_1)-receptor blocker therapy on LV remodelling in patients after MI with reduced systolic function and/or with CHF. A more complete inhibition of the renin-angiotensin aldosterone system (RAAS) by combining ACE-inhibitor and AT_1-receptor blocker therapy did not promote additional effects on cardiac volumes or LVEF and clinical outcome as compared with either therapy alone in these patients.[14]

In contrast, a subgroup analysis from Val-HeFT (Valsartan Heart Failure Trial) has shown that in patients with CHF and a reduced LVEF combination of the AT_1-receptor blocker valsartan with ACE-inhibitor therapy had a more pronounced effect on LV remodelling as compared with ACE-inhibitor therapy alone.[15] In these patients, LVEF increased, and LV end-diastolic dimension decreased significantly more with combined and prolonged RAAS blockade.[15] Furthermore, results from the CHARM (Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity) trial programme are in support of a prognostic benefit of adding the AT_1-receptor antagonist candesartan to ACE-inhibitor and ß-blocker therapy in patients with CHF and a reduced LVEF.[16]

2.2 Beta-blockers

Prolonged therapy with several β-blockers has been suggested to limit and, in a substantial proportion of patients, even to reverse LV remodelling and dysfunction after MI or in CHF. The CAPRICORN (Carvedilol Post Infarction Survival Control in Left Ventricular Dysfunction) echo substudy has demonstrated a beneficial effect of the β-blocker carvedilol on LV remodelling in patients with post-MI LV dysfunction receiving ACE-inhibitor therapy; carvedilol reduced LV end-systolic volume and improved LVEF as compared with placebo in that study.[17]

In patients with CHF, treatment with metoprolol exerted a beneficial effect on LV remodelling already after 3 months of therapy.[18] In the magnetic resonance imaging (MRI) substudy of MERIT-HF (Metoprolol Randomized Intervention Trial in Heart Failure), reverse LV remodelling was observed after metoprolol succinate therapy.[19] Similarly, carvedilol therapy reduced LV volumes and increased LVEF in patients with CHF due to ischaemic heart disease on-top-of ACE-inhibitor therapy,[20] and these changes have been suggested to explain, at least in part, improved clinical outcomes. Moreover, Metra *et al*. have reported that patients with CHF who showed a marked improvement in LVEF after 9–12 months of β-blocker therapy with metoprolol or carvedilol had an excellent prognosis, further suggesting that beneficial effects of β-blockers on LV remodelling and dysfunction are associated with improved clinical outcomes.[21] Preservation of LV function has also been observed after 5 months of bisoprolol therapy in patients with CHF and this treatment effect was related to an improved prognosis.[22] In elderly patients with CHF and advanced LV systolic dysfunction, nebivolol therapy reduced LV size and improved LVEF as reported in the echocardiographic substudy of the SENIORS (Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure) trial.[23] Taken together, there is clear evidence for these four β-blockers to exert beneficial effects on LV remodelling and dysfunction, and that these changes are related to beneficial effects on prognosis in patients with CHF.

As it is a current focus to better identify and treat patients with asymptomatic LV dysfunction in order to prevent the development of CHF, the results of the recent REVERT (Reversal of Ventricular Remodeling with Toprol-XL) study are of interest. These investigators have shown that metoprolol succinate therapy reverses LV remodelling and dysfunction in patients with asymptomatic LV systolic dysfunction.[24]

2.3 Aldosterone antagonists

Aldosterone, which is also produced by endothelial and vascular smooth-muscle cells in the heart, may exert potent detrimental effects on LV remodelling, including a stimulation of myocardial fibrosis.[25,26] In line with this concept, Chan *et al*. have recently observed in an MRI study that adding spironolactone to AT_1-receptor blocker therapy with candesartan reduces LV end-diastolic and end-systolic volumes in patients with mild-to-moderate CHF over a 1-year follow-up.[27] The observed reductions in LV volumes and mass and the improvement of LVEF suggest that spironolactone may exert beneficial myocardial structural effects.

3. Novel pharmacological approaches

3.1 Statins

While 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors, also known as statins, have a well-established role in the treatment and prevention of ischaemic coronary artery disease, their usefulness in the setting of CHF and LV dysfunction remains under investigation. In addition to a reduction in LDL, statins clearly have the potential to exert additional, 'pleiotropic' cardiac and vascular effects. Several experimental studies have shown that statins inhibit cardiomyocyte hypertrophy[28,29] and prevent LV remodelling and dysfunction in rodent models of MI[30–32] as well as in dogs with microembolization-induced CHF.[33]

One of the best characterized pleiotropic actions of statin therapy is the effect on endothelial nitric oxide synthase (eNOS) activity, that likely plays an important role in limiting LV remodelling.[34] In mice, after MI we have observed that statin therapy reduces cardiomyocyte hypertrophy and interstitial fibrosis and improves LV function to a substantially greater extent in wild-type mice as compared with eNOS-deficient mice, strongly suggesting that the effect of statins on eNOS plays an important role for statin-mediated beneficial effects on LV remodelling.[35]

An important difference between these preclinical studies and clinical trials is that patients in clinical trials are already treated, in the case of patients with CHF with ACE-inhibitors, β-blockers, and other drugs, and that the novel substance is then tested on-top-of a complex drug regime. However, in a small, randomized clinical study by Node *et al*. including 51 patients with CHF and non-ischaemic dilated cardiomyopathy, short-term (14 weeks) simvastatin therapy modestly improved LV function as examined by echocardiography and clinical status.[36] Moreover, we have observed a beneficial effect of statin therapy on endothelial nitric oxide (NO) availability in patients with CHF due to non-ischaemic cardiomyopathy, that was independent of LDL lowering, because it was not seen with the same degree of LDL reduction after ezetimibe therapy, suggesting that statin therapy augments eNOS activity in patients with CHF independent of its effects on LDL cholesterol.[37] Furthermore, in an echocardiographic study by Sola *et al*. that included 108 patients with non-ischaemic CHF and a LVEF $\leq$35%, the use of atorvastatin improved LVEF by approximately 4% and reduced LV end-diastolic diameter by $\sim$4 mm as compared with placebo.[38] Krum *et al*. have conducted a 6-month randomized placebo-controlled study of high-dose rosuvastatin in 86 patients with ischaemic or non-ischaemic CHF and a LVEF$<$40% and did not observe a significant change in LVEF as detected by radionuclide ventriculography or LV end-diastolic diameter as measured by echocardiograhy.[39] The reasons for these discrepant findings remain uncertain, but may be related to differences in the patient populations and statin doses.

In retrospective analyses, statin therapy has been associated with an improved survival in ischaemic and non-ischaemic cardiomyopathy[40] and a reduced development of CHF in patients with stable coronary disease.[41] Furthermore, high-dose as compared with moderate-dose statin therapy was associated with reduced CHF hospitalizations in patients with pre-existing CHF and an acute coronary syndrome or in patients with stable coronary disease.[42,43] In the CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure) trial that examined an elderly patient population (mean age, 73 years) with ischaemic systolic CHF, rosuvastin therapy did not significantly reduce the primary endpoint of death from cardiovascular causes, non-fatal MI, or non-fatal stroke, or reduce the number of deaths from any cause, although the drug did reduce the number of cardiovascular hospitalizations.[44] Notably, CORONA was designed to test the hypothesis that a reduction of ischaemia in ischaemic cardiomyopathy by LDL lowering and preventing the progression of coronary artery disease results in improved outcomes. The relatively low dose of rosuvastatin that was used in CORONA may not exert much of the

pleiotropic effects required for myocardial effects with impact on LV remodelling. However, the GISSI-HF (GISSI Heart Failure) trial has examined the role of statin therapy in a population with ischaemic and non-ischaemic cardiomyopathy,[45] and the results are completely neutral.

The above observations may support the notion that statins exert beneficial effects in earlier stages of heart failure and may attenuate the development of heart failure. In contrast, the benefits of statin therapy are likely limited in elderly patients with advanced CHF and established ischaemic cardiomyopathy.

3.2 Nitric oxide-cGMP signalling as a therapeutic target

The free radical gas NO, which is produced in the heart by virtually all cell types and by all three NOS isoforms, is an important modulator of cardiomyocyte function and survival besides its well known impact on the vascular system. NO at low concentrations protects cardiomyocytes from ischaemia/reperfusion-injury via soluble guanylyl cyclase activation and cGMP formation.[47–51] Moreover, NO has been shown to exert beneficial effects on LV remodelling post-MI.[46] Potential downstream targets for NO/cGMP-mediated effects in cardiomyocytes include cGMP-regulated phosphodiesterases and cGMP-dependent protein kinase type 1 (PKG I) (*Figure 1*). Previous studies have implicated PKG I in the regulation of the inotropic state, hypertrophic growth, and gene expression in cardiomyocytes after exposure to NO and other cGMP-elevating agents.[52–56] Recently, we found that PKG I protects cardiomyocytes from apoptotic cell death during ischaemia/reperfusion-injury, in part, via inhibition of TAB1-p38 signalling.[57] Takimoto *et al.*[58] have recently shown that inhibition of cGMP phospodiesterase 5A may provide an attractive pharmacological means to take advantage of the beneficial effects of cGMP. By inhibiting the breakdown of cGMP, a sustained activation of PKG I can occur thus preventing and reversing cardiac hypertrophy and remodelling.[58]

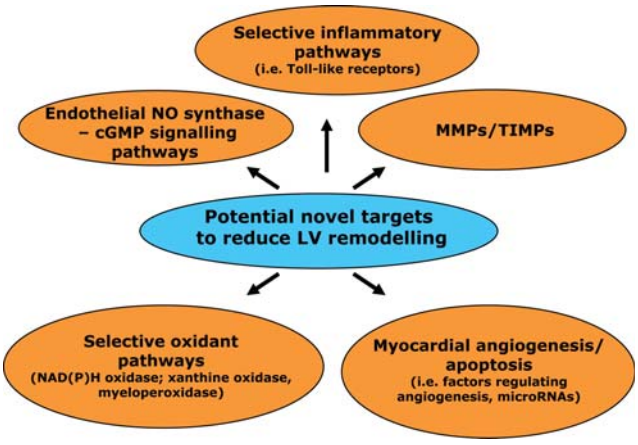

Figure 1 Nitric oxide-cGMP signalling as a potential therapeutic target. cGMP is thought to promote anti-hypertrophic/anti-remodelling effects in the heart, at least in part via cGMP-dependent protein kinase type I (PKG I) and inhibition of the calcineurin-NFAT signalling pathway. cGMP is produced via nitric oxide (NO)-stimulated soluble guanylyl cyclase (sGC) activation or natriuretic peptide-stimulation of the NPRA receptor. cGMP is degraded by phosphodiesterase 5A. sGC activators, endothelial NO synthase (eNOS) enhancers and PDE5A inhibitors (e.g. sildenafil) may be used to enhance cGMP signalling (see text for further details).

Additional approaches to stimulate NO or its signalling pathways may be the use of β-blockers with NO enhancing properties[59] or NO-enhancing drugs.[60]

Importantly, however, the source and amount of NO likely play a critical role for the effects of NO on cardiac remodelling and dysfunction. Whereas low doses of NO produced by eNOS have consistently been observed to exert cardioprotective effects in numerous preclinical studies, large amounts of NO as produced by inducible NO synthase (iNOS) have been suggested to exert detrimental effects and are not necessarily cardioprotective.[61–63] This may, at least in part, be explained by increased peroxynitrite formation, as is observed in cardiomyocyte iNOS overepressing mice.[64]

3.3 Potential targets for selective anti-oxidant therapy

Over the last years, numerous experimental studies have demonstrated a critical role of oxidant stress pathways for LV remodelling and dysfunction after MI. We have observed that mice which are deficient in the NAD(P)H oxidase subunit p47phox show a marked reduction in cardiomyocyte hypertrophy, LV dilation and dysfunction after MI[65] (*Figure 2*). Reduced MMP-2 activation and cardiomyocyte apoptosis in the infarct border zone likely contribute to the protection from LV remodelling in these mice. Moreover, in this study we have observed that cardiac xanthine oxidase activation after MI was dependent on NAD(P)H oxidase activation. Xanthine oxidase has been proposed to be involved in LV remodelling and dysfunction in several experimental and small-scale clinical studies.[66,67]

In a small clinical study, Cingolani *et al.* have observed that 1 month of therapy with the xanthine oxidase inhibitor oxipurinol improves LVEF in patients with CHF and a LVEF $<40\%$.[68] In the OPT-CHF (Oxypurinol Therapy for CHF) study, Hare *et al.* have examined the effects of oxipurinol in 402 patients with advanced systolic CHF receiving optimal medical therapy.[69] While oxipurinol did not produce clinical improvements in unselected CHF patients, a *post hoc* analysis suggested that benefits may occur in patients with elevated serum uric acid and in relation to the degree of uric acid reduction. Accordingly, serum uric acid may serve as a potential biomarker to target xanthine oxidase inhibition in CHF,[69] however, this will have to be tested in a prospective study.

Furthermore, experimental studies using myeloperoxidase (MPO)-deficient mice have suggested that leukocyte-derived, MPO-generated oxidants have a profound adverse effect on LV remodelling and function after MI.[70,71] Cardiac MPO activation may also be targeted by anti-inflammatory treatment strategies as described below.

Taken together, the present studies suggest that production of oxidant radicals by NAD(P)H oxidase, xanthine oxidase, or MPO is critically involved in LV dilation and dysfunction after MI and in CHF. However, the ideal target to interfere with myocardial oxidant stress is still to be identified.

3.4 Anti-inflammatory treatment strategies

Several studies have shown that inflammation contributes importantly to LV remodelling processes. The major challenge for an effective anti-inflammatory strategy to prevent or reverse LV remodelling is to limit detrimental inflammatory cell-mediated changes, while simultaneously

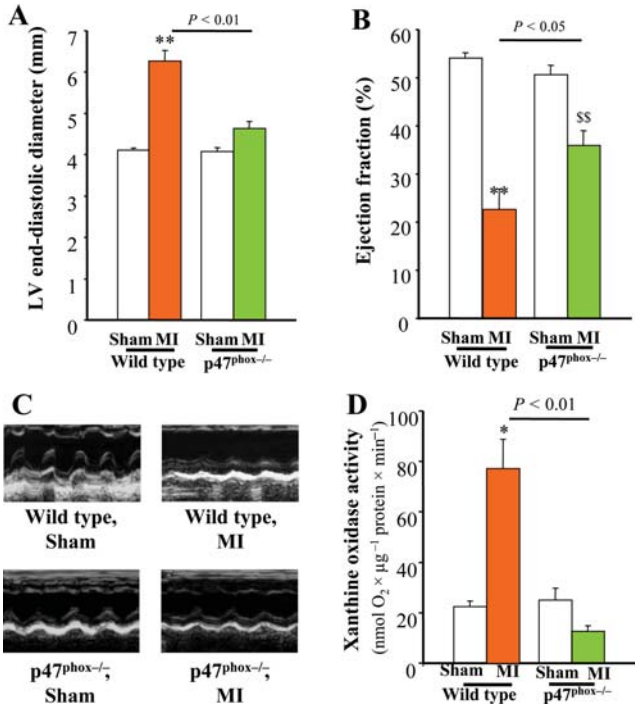

Figure 2 NAD(P)H oxidase as a potential therapeutic target: Effect of NAD(P)H oxidase subunit p47phox deficiency on left ventricular remodelling and dysfunction post-myocardial infarction (modified from[65]): (*A*) Left ventricular end-diastolic diameter of sham-operated and MI-operated wild-type and $p47^{phox-/-}$ mice. (*B*) Left ventricular ejection fraction of sham- and MI-operated wild-type mice and $p47^{phox-/-}$ mice. (*C*) Representative M-mode echocardiograms obtained from sham-operated and MI-operated mice. (*D*) Myocardial xanthine oxidase activation after MI is dependent on NAD(P)H oxidase as determined by ESR spectroscopy measurements of xanthine oxidase activity post-MI. $^{**}P < 0.01$ vs. sham WT, $P < 0.01$ vs. sham $p47^{phox-/-}$.

maintaining adequate and appropriate LV repair responses. The initial remodelling phase after MI leading to a removal of necrotic debris and to scar formation (infarct healing) should probably be considered beneficial as it serves to maintain LV structural integrity and to prevent LV rupture. Interference with the process of scar formation during the acute post-MI period, e.g. by administration of glucocorticosteroids and non-steroidal anti-inflammatory drugs (NSAID), has been suggested to result in increased thinning of the infarct zone and potentially greater degrees of infarct expansion. Therapy with NSAIDs (ibuprofen and indomethacin) in the early post-MI period resulted in an increased thinning of the infarct zone in experimental studies.[72,73] More recently, Timmers *et al*. have reported that therapy with the COX-2 inhibitor celecoxib increased mortality and enhanced LV remodelling and dysfunction in a pig model after MI.[74]

In contrast, studies in rodent models, such as in rats after MI,[75] have reported beneficial effects of COX-2 inhibition on LV dysfunction when therapy was started late after MI. In a recent study in a rodent model, Fang *et al*. examined inflammatory cell infiltration, MMP-9 activation, and the risk of cardiac rupture after MI.[76] Inflammatory cell infiltration was greater in male as compared with female mice and was associated with a higher risk of cardiac rupture, potentially due to increased MMP-9 activation.[76] Moreover, several recent experimental studies have suggested that specific anti-inflammatory interventions may exert potent beneficial effects on LV remodelling and dysfunction, raising the possibility that an appropriately timed and targeted anti-inflammatory therapeutic intervention may exert beneficial effects on LV remodelling and dysfunction.

3.4.1 Innate immunity-toll-like receptors

Toll-like receptors (TLRs), primary innate immune receptors that are also activated by endogenous signals, such as oxidative stress and heat shock proteins, are expressed by cardiomyocytes and vascular cells. Of note, LV dilation and dysfunction, mortality, and myocardial fibrosis in the non-infarcted area were markedly attenuated in TLR-2-deficient mice after MI.[77] Furthermore, two recent experimental studies have observed that TLR-4 activation, that is increased in the failing myocardium, is an important mediator of maladaptive LV remodelling and dysfunction and reduced survival after MI.[78,79] These studies suggest a causal role of TLR-2 and -4 activation in post-MI maladaptive LV remodelling, likely mediated via stimulation of pro-inflammatory cytokine production and matrix degradation. TLRs may therefore constitute a novel treatment target to prevent LV remodelling and dysfunction. Complete inhibition of these pathways may yield undesired effects due to functional loss of this innate immune mechanism, however, partial inhibition for a limited time period may be beneficial and should be further explored.

3.4.2 Interleukin-1 receptor antagonists

A recent experimental study has shown that exogenous administration of a recombinant human interleukin (IL)-1 receptor antagonist (anakinra) can reduce cardiomyocyte apoptosis and LV remodelling after acute MI.[80] Ikonomidis *et al*. have reported antioxidant effects and improved LV function after short-term anakinra therapy in 23 patients with rheumatoid arthritis.[81] A more detailed understanding of the role of specific inflammatory pathways for LV remodelling may provide interesting novel opportunities for therapeutic interventions to prevent or reduce LV remodelling. In this context, several factors have recently been identified, either by microarray approaches or elucidation of paracrine factors released from stem cells, that are involved in the modulation of inflammation and cardiac repair mechanisms post-MI. Growth-differentiation factor-15, for example, is produced in the infarcted and failing heart and has been shown to identify patients at high risk for adverse cardiovascular events.[82–85] Moreover, frizzled-related protein 2 has been shown to markedly attenuate the remodelling process after MI.[86]

3.5 Selective matrix-metalloproteinase inhibition

MMPs are a family of proteolytic enzymes promoting extracellular protein degradation in the cardiovascular system. They have been shown in several experimental studies to participate in the complex remodelling processes of the myocardium after MI and in CHF.[87] The biological activity of MMPs is regulated at different levels, i.e. gene expression, activation of precursor proenzyme forms, and inhibition by endogenous tissue inhibitors of MMPs, the tissue inhibitor of metalloproteinases (TIMPs). Notably, plasma TIMP-1 (tissue inhibitor of metalloproteinase-1) and

MMP-9 have been identified as indicators of LV remodelling and prognosis in patients after acute MI.[88]

Selective MMP inhibition has been shown to reduce LV remodelling without inhibiting angiogenesis after MI in experimental models.[89] In the PREMIER (Prevention of Myocardial Infarction Early Remodelling) trial,[90] the first human therapeutic study with an MMP inhibitor in patients after MI, 253 patients with first ST-segment elevation MI (LVEF $<40\%$) were randomized to placebo or the oral MMP inhibitor PG-116800, that previously exerted significant anti-remodelling effects in animal models of MI and ischaemic CHF.[91] However, after 90 days of follow-up no significant effects on LV remodelling or clinical outcome were noted in that study.[90] PG-116800 is a MMP inhibitor of the hydroxamic acid class with high affinity for MMP-2, -3, -8, -9, -13, and -14 and low affinity for MMP-1 and -7.[90] Notably, an experimental study by Spinale *et al*. has demonstrated that MMP inhibition conferred a beneficial effect on survival early post-MI, but that prolonged MMP inhibition was associated with higher mortality rates and adverse LV remodelling, suggesting that there may exist an optimal time window with respect to pharmacological interruption of MMP activity in the post-MI period.[92] In support of this concept, Kelly *et al*. have observed a biphasic profile of plasma MMP-9 that is related to LV remodelling and function in patients after MI.[93] Higher early levels of MMP-9 were associated with the extent of LV remodelling. In contrast, higher plateau levels late after MI were associated with a relative preservation of LV function. Therefore, the temporal profile, rather than the absolute magnitude, of MMP-9 activity appears to be important for LV remodelling after AMI,[93] and likely is important for potential novel therapeutic strategies.

3.6 Angiogenesis and/or stem cell transfer

Coronary angiogenesis is enhanced during the acute phase of adaptive cardiac growth but is reduced as hearts undergo maladaptive remodelling.[94–96] Coronary angiogenesis is associated with the induction of myocardial VEGF and angiopoietin-2 expression, while inhibition of angiogenesis leads to a decreased capillary density, contractile dysfunction, and impaired cardiac growth. Endothelium- and cardiomyocyte-derived factors are involved in cardiac angiogenesis.[95] Thus, both cardiac size and function are angiogenesis dependent, and disruption of coordinated tissue growth and angiogenesis in the heart may contribute to the progression from adaptive cardiac hypertrophy to CHF.

Recent observations indicate that stem and progenitor cells can release pro-angiogenic factors which in turn, stimulate angiogenesis in the border zone post-MI. Increased myocardial angiogenesis after stem and progenitor cell transfer has been postulated to improve infarct healing and energy metabolism in the infarct border zone.[97–100] Early clinical trials suggest that intracoronary delivery of bone marrow cells may improve LVEF recovery in patients after MI.[101] More work is needed, however, to identify the most suitable cell types and application methods and to define the impact of cell therapy on clinical endpoints and other indices of LV remodelling, i.e. LV end-diastolic volumes. Furthermore, other delivery strategies for pro-angiogenic factors after MI and in CHF need to be explored.

4. Conclusions

LV remodelling remains an important treatment target in patients after MI or with CHF. While the beneficial effects of ACE inhibition, AT_1-receptor blocker therapy, and β-blocker therapy on LV remodelling are established, adverse LV remodelling is still observed in a substantial proportion of patients and is related to an adverse prognosis. These observations call for novel therapeutic strategies. Based on recent insights into the mechanisms leading to LV remodelling, novel therapeutic targets have been proposed, e.g. eNOS-derived NO availability, activation of cardiac and leukocyte-dependent oxidant stress pathways, and activation of inflammatory pathways and MMPs. It is hoped that these experimental observations will eventually be translated into new and successful treatment strategies in the clinical arena.

Conflict of interest: none declared.

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